

Complete Summary

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GUIDELINE TITLE

Evidence based clinical practice guideline of fever of uncertain source. Outpatient evaluation and management for children 2 months to 36 months of age.

BIBLIOGRAPHIC SOURCE(S)

Cincinnati Children's Hospital Medical Center. Evidence-based clinical practice guideline of fever of uncertain source. Outpatient evaluation and management for children 2 months to 36 months of age. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2000. 10 p. [36 references]

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SCOPE

DISEASE/CONDITION(S)

Fever of uncertain source, characterized as a temperature of 38.0 degrees C (100.4 degrees F) or higher, of cause that is not apparent after a thorough history and physical examination.

GUIDELINE CATEGORY

Evaluation
Management
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Infectious Diseases
Internal Medicine
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To help practitioners estimate risks for occult bacterial infections and provide options for outpatient evaluation and management.

TARGET POPULATION

These guidelines are intended primarily for use in children aged 2 months through 36 months presenting with fever of at least 38 degrees C (100.4 degrees F) and without a focal source for the fever found by history and physical exam.

Exclusions: These guidelines are not intended to address all considerations that are needed to manage the following categories of patients:

- Child with a fever source found on history or physical exam
- Child that is clinically "toxic"
- Child with petechiae
- Child with an immunodeficiency syndrome
- Child with chronic illnesses, altering care options
- Child on antibiotics
- Child given diphtheria-pertussis-tetanus immunizations within 48 hours
- Child presenting with seizures
- Child requiring intensive care management

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment

1. Physical examination, including use of the Yale Observation Scale.
2. Patient history targeted to determination of immunization status and exposures to infectious agents and observation of behavioral changes.
3. Laboratory tests: Urinalysis and sterile urine culture, white blood cell count, complete blood count, absolute neutrophil count, and blood culture.

Treatment

1. Antibiotic therapy: Amoxicillin or ceftriaxone, or in combination, and alternative antibiotics when required.

2. Observation at home prior to initiating antibiotic therapy.

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of laboratory tests and clinical assessment methods, including the Yale Observation Scale
- Risk of serious bacterial infection in a febrile child

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

36 source documents

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Based Grading Scale:

A: Randomized controlled trial: large sample

B: Randomized controlled trial: small sample

C: Prospective trial or large case series

D: Retrospective analysis

E: Expert opinion or consensus

F: Basic laboratory research

S: Review article

M: Meta-analysis

Q: Decision analysis

L: Legal requirement

O: Other evidence

X: No evidence

METHODS USED TO ANALYZE THE EVIDENCE

Review

Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Articles were divided among team members, with two or more members assigned to the same articles to assure that results were analyzed from several different perspectives.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations contained in this document were formulated by a working group that included community and hospital based physicians, nurses, respiratory therapists, and others, who examined current local clinical practices and performed extensive and critical literature reviews.

During formulation of these guidelines, the committee members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines have been reviewed and approved by Children's Hospital Medical Center senior management, Legal Services, the Institutional Review Board, the hospital's Pharmacy and Therapeutics, Clinical Practices, Executive, and other committees and individuals as appropriate to their intended purposes.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

Each recommendation is followed by evidence grades (A-X) identifying the type of supporting evidence. Definitions of the evidence grades are presented at the end of the Major Recommendations field.

Clinical Assessments

The Telephone Encounter

1. When contacted by telephone, it is recommended that a practitioner consider physically assessing any febrile child when verbal descriptions are unclear and the degree of illness uncertain.

Temperature and Fever

2. Fever is usually defined as a temperature of at least 100.4 degrees F (38 degrees C) rectally (see Table 1 in the original guideline document for definitions used in the guideline). Although rectal temperatures are more accurate, it is recommended that a practitioner give credence to a parent's verbal report of a child's fever measured by any method, including when detected only by touch. A fever detected only by touch is reported to have a sensitivity of 84% and specificity of 76% (Hooker, 1993 [C]; Reisinger, Kao, & Grant, 1979 [C]; Graneto & Soglin, 1996 [C]).

Assessing the Degree of Illness

3. Both subjective and objective measures are recommended to estimate the degree of illness.
 - Note 1: The following features are included in the objective Yale Observation Scale. They are recommended for consideration in this assessment to supplement practitioners' subjective impressions (see Table 2 in the original guideline document for the Yale Observation Scale) (Teach & Fleisher, 1995 [A]).
 - Cry quality
 - Reaction to parent
 - State of alertness
 - Color
 - Hydration
 - Interactive behaviors

- Note 2: The sicker a febrile child appears, the more likely the fever is associated with a serious bacterial infection (Teach & Fleisher, 1995 [A]).

Well appearing	<3% chance of serious bacterial infections
Ill appearing	26% chance of serious bacterial infections
Toxic	92% chance of serious bacterial infections

- Note 3: Response to antipyretics is not a reliable predictor of illness severity (Kuppermann, 1999 [S,E]).

Identifying Overt Focal Infections

History

4. It is recommended that history be targeted to determine the child's immunization status and exposures to known infectious agents. This information, with knowledge of disease prevalence in the community, will help establish the likelihood of specific causes of fever, and particularly those of viral origin.
 - Note 1: Less than 1 out of 100 viral infections is associated with a bacterial infection (Kuppermann et al., 1997 [C]; Greenes & Harper, 1999 [C]; Liebelt, Qi, & Harvey, 1999 [D]).
5. It is recommended that history also be targeted to determine if behavioral changes caused by some focal infections have been observed. These include, but are not limited to, the ear pulling of otitis media, coughing of pneumonia, vomiting of gastroenteritis, or crying with voiding associated with some urinary tract infections.

Physical Examination

6. Because occult bacteremia can occur with focal infections, it is recommended that when a source of infection is identified on physical examination, further evaluations be considered whenever the practitioner judges that focal findings are insufficient to explain the degree of the child's fever and illness.

Identifying Occult Focal Infections

7. Using current technology and evidence, there are no perfect methods for detecting all possible occult infections. There also are no methods for identifying with absolute certainty which specific child is among the very few with a serious bacterial infection. It is recommended that the extent of evaluation to determine if a particular child has an occult infection, be based in part on each individual practitioner's level of comfort with the child's degree of illness. These approximations result from subjective and objective physical findings as supplemented by selected laboratory results. In addition, it is appropriate to include in the decisions a family's apparent tolerance for risk, the likelihood that identification of the source of fever will modify

management, and the likelihood of good outpatient follow-up [Evidence Grade: Local expert opinion].

Urinary Tract Infections (UTIs)

8. When evaluating infants presenting with fevers of uncertain source, it is recommended that a practitioner have a low threshold for obtaining a urinalysis and urine culture using sterile collection technique (Bauchner et al., 1987 [C]). This recommendation is strongest for the youngest infants. It also applies to older children with clinical signs and symptoms suggesting a urinary tract infection.
 - Note 1: The prevalence of urinary tract infections in infants and young children 2 months to 2 years of age who have no fever source evident from history or physical examination is estimated to be about 5% (American Academy of Pediatrics [AAP], 1999 [E,S]).
 - Note 2: Consistent clinical findings range from being generally nonspecific in the infant, to very evident voiding dysfunction in the older child (see Table 3 in the guideline document for clinical signs and symptoms of urinary tract infection).
 - Note 3: The prevalence of urinary tract infection in febrile girls age 2 months to 2 years is more than twice that in boys (relative risk, 2.27). The prevalence of urinary tract infection in girls younger than 1 year of age is 6.5%; in boys, it is 3.3%. The prevalence of urinary tract infection in girls between 1 and 2 years of age is 8.1%; in boys, it is 1.9%. The rate in circumcised boys is low, 0.2% to 0.4%. The rate in uncircumcised boys is 5 to 20 times higher than in circumcised boys (AAP, 1999 [E,S]).
9. It is recommended that any positive urinalysis result be considered consistent with a presumptive diagnosis of urinary tract infection and an indication to initiate antibiotic therapies and other measures fully described in the Children's Hospital Medical Center guideline titled "[Evidence Based Clinical Practice Guideline for Patients 6 Years of Age or Less with a First Time Acute Urinary Tract Infection](#)" (March, 1999).
 - Note 1: Any one of the following study results defines a positive urinalysis. These tests have sensitivities varying between 30-50% and specificities of 75-85%. A positive culture on urine collected using sterile technique remains the only standard for diagnosing a definite urinary tract infection (Craig et al., 1998 [C]; Hoberman et al., 1994 [C]).
 - Positive nitrite screen.
 - Positive leukocyte esterase.
 - Positive microscopic examination. Positive if >10 white blood cells/hpf (spun sample) or organisms visible in unspun sample or on Gram stain. More sensitive and specific than other urine screening tests but not readily available (Hoberman et al., 1994 [C]).

Pneumonia

10. Pneumonia is seldom occult. It is recommended that pneumonia be considered when a fever exceeds 39 degrees C (102.2 degrees F) or a white blood cell count exceeds 20,000 mm³ (Bachur, Perry, & Harper, 1999 [C]).

- Note 1: In children with lower temperatures and cell counts, the absence of respiratory distress, tachypnea, rales (crackles), or decreased breath sounds reduces the likelihood of pneumonia (Jadavji et al., 1997 [Canadian guideline]).
- Note 2: Age is a predictor of the cause of pneumonia. Viral pneumonia is most common during the first 2 years of life (Jadavji et al., 1997 [Canadian guideline]).
- Note 3: Chest x-rays do not often help in the choice of appropriate pneumonia therapy (McCarthy et al., 1981 [C]).
- Note 4: Pneumonia and bacteremia are infrequently associated (<3%) (Hickey, Bowman, & Smith, 1996 [C])

Bacterial Gastroenteritis

11. Gastroenteritis due to any cause is rarely occult and almost always signaled by some combination of diarrhea and vomiting.
 - Note 1: Rotavirus is the most common cause of acute gastroenteritis in children (AAP, 1996 [S,E]).
 - Note 2: Bloody or mucoid stools usually herald bacterial gastroenteritis. There is also increased likelihood if there is a history of foreign travel or occurrence during a specific pathogen community outbreak (Limbos & Lieberman, 1995 [S,E]; Kuppermann, 1999 [S,E]).
12. Typical gastroenteritis usually responds well to supportive care. The management and specific recommendations for children with gastroenteritis are detailed in the Children's Hospital Medical Center guideline titled "Evidence Based Guidelines and Recommendations for the Community Evaluation and Medical Management of Children with Acute Gastroenteritis" (1997).

Meningitis

13. Although bacterial meningitis is sometimes occult in the ill-appearing febrile infant or very young child, bacterial meningitis is usually suspected by clinical exam (e.g., neck stiffness, lethargy, vomiting), and diagnosed by lumbar puncture and the characteristics of the spinal fluid.

Identifying Occult Bacteremias

14. It is recommended that febrile children be assessed to approximate their risk of being one of the <3% with occult bacteremia (Lee & Harper, 1998 [C]).
 - Note 1: Risks are low but modified by height of fever and patients age. The risk for occult bacteremia is increased if more than one risk factor is present (Kuppermann, Fleisher, & Jaffe, 1998 [A]; Lee & Harper, 1998 [C]).

See the original guideline document for a table of fever as a predictor of occult bacteremia and a graph of age as a predictor of pneumococcal disease in a febrile child.

Laboratory Studies and Detection of Occult Bacteremia

15. In spite of well appearance, a small proportion of febrile children might have bacteremia, it is not always necessary to obtain laboratory studies immediately for children appearing well and with clinical characteristics consistent with a low risk for bacteremia. If the family understands, agrees, and has the resources to assure medical follow-up, a low risk child might be considered a candidate for observation at home with daily reassessments until the fever resolves (Woods et al., 1990 [D]; Kuppermann, 1999 [S,E]; Local expert opinions).
16. When a child appears ill, or there is any uncertainty about a child's condition or risk status, laboratory studies are recommended. Studies strongly recommended for consideration include urinalysis, sterile urine culture, complete blood count, white blood cell count, and absolute neutrophil count (Kuppermann, 1999 [S,E]; Local expert consensus) (see the original guideline document for a graph of white blood cell count as a predictor of occult bacteremia).
 - Note 1: A white blood cell count of $>15,000/\text{mm}^3$ raises risk for bacteremia to 3-4%. If $>20,000/\text{mm}^3$, the risk is 8-10%.
 - Note 2: An absolute neutrophil count is more sensitive and specific than a white blood cell or absolute band count for occult bacteremia detection. An absolute neutrophil count of $>10,000/\text{mm}^3$ raises risk, to 8-10% (Kuppermann, Fleisher, & Jaffe, 1998 [A]; Lee & Harper, 1998 [C]).
17. Because 6% to 10% of children with bacteremia may develop serious bacterial infections, it is recommended that a blood culture also be considered especially if the child is ill appearing or the degree of illness is uncertain. This recommendation is particularly strong if antibiotic therapy is to be started.
 - Note 1: Blood culture of a single large blood volume is more likely to grow organisms than multiple cultures on smaller volumes (Kuppermann, 1999 [S,E]; Isaacman et al., 1996 [C]).
18. There is no published evidence demonstrating that chest x-rays, stool cultures, and lumbar puncture are helpful as "routine" studies. No specific recommendations are made other than to consider these studies when there are specific indications that the child is likely to have occult or complicated pneumonia, gastroenteritis, or meningitis (Kuppermann, 1999 [S,E]).

Treatment for Occult Bacteremia

19. Children who appear well, are judged to be at sufficiently low risk to preclude the need for laboratory studies, and have a high likelihood of excellent follow-up can often be considered candidates for observation at home without starting antibiotic therapy [Evidence Grade: Local expert opinion].
20. If because of history, physical, and laboratory assessments, a child is judged to be at high risk of being among the $<3\%$ of febrile children with occult bacteremia, starting empiric antibiotic therapy is considered a reasonable option after obtaining appropriate samples for culture (Local expert consensus).
 - Note 1: This recommendation is strongest for ill appearing children pending clinical responses and return of bacterial culture results. This is especially recommended for those with white blood cell count $>15,000/\text{mm}^3$ or an absolute neutrophil count $>10,000/\text{mm}^3$.
 - Note 2: Although complications are rare and up to 75% of occult pneumococcal bacteremia resolve spontaneously, children with occult

bacteremia and treated with antibiotics clinically improve earlier and are less likely to be bacteremic at follow-up. An element of uncertainty is acknowledged, however, and it is estimated that a practitioner would need to treat 19 patients with suspect bacteremia for each patient subsequently documented to have actual bacteremia (Kuppersmann, 1999 [S,E], local expert opinions).

- Note 3: A decision to use antibiotics and the specific choice of antibiotic must be balanced against the increasing emergence of bacterial resistance. Also, in spite of a prevalent practice of starting empiric oral or parenteral antibiotics in febrile patients to try to prevent complications, the efficacy for this practice has never been documented in a randomized controlled fashion (Rothrock et al., 1998 [M]; Kuppersmann, 1999 [S,E]).

21. Based on the 90% predominance of *Streptococcus pneumoniae* as a likely organism, it is recommended that initial antibiotic choices referentially include only amoxicillin or ceftriaxone, or both in combination. There are no consistent evidences that one or the other of these choices is more efficacious (Fleisher et al., 1994 [A]).

Note: See the original guideline document for a table of antibiotic dosing, and a discussion of the issue of resistance and the use of "high dose" amoxicillin.

- Note: For patients with likely allergies to the preferred antibiotics, no alternative antibiotics have been documented to be more efficacious. It is recommended that alternative drug choices be based on bacterial cultures and antibiotic sensitivities. Consultation with a specialist in pediatric infectious diseases might also be considered.

22. It is recommended that deferring antibiotic treatment pending a period of observation at home also be considered a valid management option for selected patients who look well, have normal laboratory studies, and with high likelihood of excellent follow-up.

23. It is recommended that, with the exception of special situations, if a decision is made to treat with antibiotics, the therapy be discontinued if cultures are reported as being negative.

24. If a blood culture is returned as being positive or fever is persistent, reexamination is recommended to reassess for the possibility that bacteremia was due to a previously undetected focal infection such as meningitis. It is recommended that the decision about whether to start or change antibiotics and whether to follow the child as an inpatient or outpatient be based on the current condition of the child and the organism isolated (Kuppersmann, 1999 [S,E]).

Evidence Based Grading Scale:

A: Randomized controlled trial: large sample

B: Randomized controlled trial: small sample

C: Prospective trial or large case series

D: Retrospective analysis

E: Expert opinion or consensus

F: Basic laboratory research

S: Review article

M: Meta-analysis

Q: Decision analysis

L: Legal requirement

O: Other evidence

X: No evidence

CLINICAL ALGORITHM(S)

An algorithm summarizing the recommendations for the evaluation and treatment of fever of uncertain source in 2 to 36 month old children is provided in the guideline document.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is identified and graded for each recommendation (see "Major Recommendations"). In the guideline document, each cited reference is graded individually.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Effective medical assessment and management of children aged 2 months to 36 months of age with a fever of uncertain source.

POTENTIAL HARMS

A decision to use antibiotics and the specific choice of antibiotic must be balanced against the increasing emergence of bacterial resistance.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

These recommendations result from the review of literature and practices current at the time of their formulations. This protocol does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to this pathway is voluntary. The physician, in light of the individual circumstances presented by the patient, must make the ultimate judgment regarding the priority of any specific procedure.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The implementation process for each Children's Hospital Medical Center guideline is a phase in a larger process of Guideline Development. This process is utilized for every guideline but is not addressed in the content of every guideline.

At the start of each guideline, a projected implementation date is determined. Reservations for education are then made (Grand Rounds, Patient Services, Inservices). When the guideline is complete and enters into the Approval Process, Education planning begins. Changes created by the guideline are outlined as well as anticipated outcomes. The implementation date is confirmed, and Education is provided. The guideline is implemented and pilot information collection started. The Guideline Coordinator makes daily rounds and eligible children are followed to document the use of the guideline. The implementation phase aids in finding areas for improvement or question. When issues identified are improved, the guideline progresses to the monitoring phase.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Cincinnati Children's Hospital Medical Center. Evidence-based clinical practice guideline of fever of uncertain source. Outpatient evaluation and management for children 2 months to 36 months of age. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2000. 10 p. [36 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Feb

GUIDELINE DEVELOPER(S)

Cincinnati Children's Hospital Medical Center - Hospital/Medical Center

SOURCE(S) OF FUNDING

Cincinnati Children's Hospital Medical Center

GUIDELINE COMMITTEE

Fever of Uncertain Source Team

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available from the [Cincinnati Children's Hospital Medical Center](#).

For information regarding the full-text guideline, print copies, or evidence-based practice support services contact the Children's Hospital Medical Center Health Policy and Clinical Effectiveness Department at HPCEInfo@chmcc.org.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on March 15, 2001. The information was verified by the guideline developer as of June 15, 2001.

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